IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Application of Sham Chopra.	: Group Art Unit: TBA
Appln. No.: TBA	: Examiner: TBA
Filed: TBA	:
For: **CHEMICAL DELIVERY DEVICE**	:

Assistant Commissioner of Patents
Washington, D.C. 20231

SIR:

DETAILED DISCUSSION OF REFERENCES

Two searches of the prior art disclosing sustained release drug delivery devices comprising a geometrically shaped core with at least one planar face, at least one chemical compound and at least one polymer dispersed within the core and a coat that takes longer to disintegrate than the core takes to dissolve, and covers all the faces of the core except the exposed face(s). One search in the US patent office covered class 424/subclasses 468, 472, 473, 474, 475, 479, 480, 481, 482. A second search was carried out in Chemical Abstracts, USPATFUL, Derwent WPI (class A61K), the European Patent Office (class A61K9/20-32: pills with coating and controlled release) and US classification 424/480. Search terms include: controlled release, (shaped) core, (partial, external etc) polymer coating, aperture, hole, etc.; planar (release) face/surface. A subsequent search of coatings comprised of an insoluble polymer and water soluble pore-forming elements was conducted in the USPTO (see below).

The closest prior art to the present references appear to be the patents described below.

Ashok Shah, *et al.*, U. S. Patent No. 5,922,342 (the '342 patent)

The invention provides a controlled release composition comprising (i) a compressed core containing a drug which core has two planar parallel surfaces and (ii) an impermeable coating surrounding the core except for the planar surfaces. The parallel surfaces afford zero order release by maintaining a constant surface area during the drug delivery process.

The compressed core and planar surfaces can be of various shapes including circular, elliptical and polygonal (i.e. triangular and hexagonal cores are depicted in Fig. 5-10; col. 3, lines 25-38). The core consists of at least 90% of non-disintegrating therapeutic agent (col 3, lines 4-6 and col.4, lines 45-47). Rumen boluses contain up to 50% w/w non-disintegrating therapeutic agent (col. 3, lines 39-45). This

difference reflects the provision for a quantity of a metal or dense substance (i.e. a weight) to assure retention of a bolus in the rumen. This does not reflect a change in the core design.

The seal is an impermeable film forming compound capable of protecting the non-coated surfaces of the core from dissolution and can consist of materials such as polyvinyl chloride, polyvinyl acetate, ethyl cellulose, polyurethanes, cellulose acetate, poly(alkyl methacrylate) and cellulose. (col. 5, lines 23-29)

Methods for preparing the devices are described. Compressed cores were prepared on a Carver Press (Example 1) and coating was accomplished with an Elanco capsule sealing machine (col. 5, lines 35-37 or rolled in a trough containing coating materials (col. 5, line 43-45).

Present Invention	U. S. Patent No. 5,922,342
The compositions in claims **1**, **22** and **37** have a coating comprised of an insoluble polymer and soluble pore forming materials which dissolve after the core is depleted producing a permeable porous coating that can disintegrate.	Impermeable coating deposited from film-forming material covers core with no provision for pore-forming granules. The coating will not disintegrate after the core is depleted.
The compositions in claim **22** (Fig. 3-5) afford increasing or decreasing release rates of active ingredient from dissolution devices during the delivery period.	The compositions are cylindrical or polygonal and have constant surface area affording only zero-order kinetics. No geometries resembling Fig 3-5 are disclosed.
Core contains < 90% active therapeutic agent.	Core contains ≥ 90% active therapeutic agent.
The compositions in claim **34** have a core containing insoluble polymers (i.e., diffusion controlled devices) and are designed to afford increasing surface area to maintain zero order kinetics (Fig 3-5).	Insoluble polymer matrices are not disclosed. The core contains at least 90% soluble material.

Chopra *et al.*, U. S. Patent No. 5,342,627 (the '627 patent)

The invention discloses a controlled release composition comprising (i) a shaped core with a cylindrical exposed face wherein at least one dimension of the exposed surface changes as the active component dissolves maintaining a constant exposed surface area and (ii) a covering impermeable to the active substance and the fluid medium surrounding the core except for the cylindrical exposed surface.

The architecture of the disclosed device is complex and the only specific dimensions exemplified have the diameter, DC, of the bore **3** [is] equal to the thickness, Hp, of the cylindrical face **4** (col. 10, lines 51-55 and Fig. 1a). Although dissolution (Examples 1-6) and diffusion (Example 7-8) devices are described, different geometries are required for zero-order release and only one (corresponding to a zero-order dissolution device) is described. The invention discloses that the cavity walls of the diffusion device can be concave, convex or linear, but no addition geometries are exemplified. The specification also suggests that the geometrical profile of the cavity and core of the diffusion device may be changed to provide bursts at specific times during the dissolution profile (col. 5, lines 28-38). The shaped core comprising active substance disposed, preferably uniformly, in a matrix of an inert excipient insoluble in the fluid, said device

being axial symmetrical, with said aperture being peripherally disposed so that the release surface of core which is exposed through said aperture is substantially cylindrical or part of a cylinder in shape (col. 4, lines 30-36).

The impermeable coating may contain binders, lubricants colors, flavorings and plasticizers (col 7, lines 6-22). Coatings were applied to the core using a compression-coating machine (col. 6, line 51 to col. 7, line 5).

Present Invention	U. S. Patent No. 5,342,627
The compositions in claims 1, 22 and 37 have a coating comprised of an insoluble polymer and soluble pore forming materials which dissolve after the core is depleted producing a permeable porous coating that can disintegrate.	Core covered by impermeable coat. Coating can include binders, lubricants colors, flavorings and plasticizers but pore-forming particles are not disclosed.
All the dimensions of the exposed surface(s) in the compositions of claim 1 have constant dimensions during the delivery period.	Dissolution architecture (e.g. claim 1(a)) requires change in at least one dimension of the exposed surface to afford constant surface area during delivery period.
Novel architectures for variable release rate dissolution devices are disclosed in FIG. 3-5. (Claim 22)	Dissolution devices with variable release rates and diffusion devices with constant release rates require changes in the exposed surface (or dissolution front) area which are not enabled. The application only alludes to devices capable of programmed bursts of the active ingredients. The diffusion device in claim 1(b) requires increasing surface area to maintain zero-order release but disclosed dimensions provide constant surface area. No dimensions or description for a variable release composition are disclosed. Complex architecture affords limited opportunity for modifying the dimensions without introducing mechanical instability.
Novel architectures for constant release rate diffusion devices are disclosed in FIG. 3-5. (Claim 37)	
Only devices in FIG. 1b, 3 and 4 are axially symmetric but their exposed surface is circular, not cylindrical.	Core has axial symmetry and aperture is substantially cylindrical or part of a cylinder in shape

R. B. DePrince U. S. Patent No. 4,663,147 (the '147 patent)
J. N. McMullen U.S. Patent No. 4,816,262 (the '262 patent)
C. Kim U.S. Patent No. 6,110,500 (the '500 patent)

The '147, '262 and '500 patents disclose a controlled release tablet with a (i) cylindrical core containing a central bore and (ii) a hydrophobic coating on all surfaces except the central bore.

The '147 patent discloses a diffusion device which comprises a disk which is composed of a uniform mixture of a diffusible active ingredient and a polymer which is insoluble in and impermeable to the fluid medium and impermeable to the diffusible active ingredient, wherein the surfaces are coated with a polymer which is insoluble in and impermeable to the fluid medium with the exception of one or more apertures which extend through the disk (col. 2, lines 47-57). The device is a diffusion device since the

active ingredient is incorporated into an insoluble polymer matrix. The geometry is designed such that the ratio of the surface area of the diffusible solid exposed to the fluid medium to the length of the path through which the exposed solid must diffuse to exit the disk is substantially constant and therefore produces zero-order release kinetics (col. 4, lines 4-7).

In McMullen's device the thickness of the core increases gradually from the central bore to the periphery. The core consists of at least a hydrophilic releasing agent (i.e, a hydrophilic drug) (col. 1, lines 62-63). Alternatively the core is composed of a fused matrix of an active ingredient (sodium salicylate) and a polymer matrix (polyethylene) (col. 4, lines 39-43 and Example 1) The upper and lower annular faces and the outer cylindrical faces are all coated with a continuous hydrophobic material so that the hydrophilic material can only be released through the center bore (col. 2, lines 61-65). The central core is formed from a solid mixture that includes a hydrophilic active compound (col. 2, lines 52-54). A minimum core volume is necessary which requires addition of inert soluble filler when the drug concentration is low. The core can incorporate pure active compound but the release rate is faster and bore size must be changed to control the release rate (col. 4, lines 29-37). The device can be a diffusion or dissolution device although the release rate of a pure compound in a dissolution device was difficult to control . The surface area at the release surface increases as it moves toward the periphery (i.e. as the height and the radius increase) and therefore zero-order release should be difficult to achieve in a dissolution mode.

Kim describes a similar cylindrical device with a (i) core containing a hydrophilic, water-soluble polymeric carrier with a central bore, and, (ii) a hydrophobic coating covering the entire core except the central bore. Unlike the device in the '262 patent, the thickness is constant. This release rate is controlled by erosion of the hydrophilic polymer in the core (col. 3, lines 18-19). Swelling of these hydrophilic polymers also can influence the release rate (col. 3, line 64 to col.4, line 2).

Two processes for manufacturing the delivery device are disclosed. "Donut" shaped tablets can be prepared with a standard Carver press and subsequently coated. Alternatively, a solid tablet can be prepared and coated and a hole subsequently drilled through the center.

Present Invention	U. S. Patent No. 6,110,500
Core is any combination of soluble or insoluble active ingredient a dissolution regulator and/or an insoluble polymer matrix. Release of active compound does not depend on swelling of the core	The core of the '500 patent is a swellable/gellable polymer which is unrelated to the present device.

Present Invention	U. S. Patent No. 4,663,147 U. S. Patent No. 4,816,262
Present invention can accommodate dissolution or diffusion methodologies according to the physical and chemical properties of the active ingredient. Both hydrophobic and hydrophilic active compounds can be incorporated into diffusion or dissolution devices.	The '262 device is a dissolution device. The '147 device is a diffusion device. The '262 patent is design for a hydrophilic active compound.
The dimensions, and therefore the surface area, of the exposed face(s) can be adapted to dissolution or diffusion devices.	Dimensions of the '262 device require that the radius and height of exposed surface both increase as dissolution proceeds. This geometry is only appropriate for a diffusion device and results in nonlinear release from a dissolution device.
The compositions in claims **1**, **22** and **37** have a coating comprised of an insoluble polymer and soluble pore forming materials which dissolve after the core is depleted producing a permeable porous coating that can disintegrate.	Impermeable coating deposited from film-forming material covers core with no provision for pore-forming granules. The coating will not disintegrate after the core is depleted.
The exposed surface(s) are circular, not cylindrical as in the '147 and '262 patent	The aperture is substantially cylindrical.
Two exposed surfaces on the periphery of the device and on opposite sides of the device.	The circular bore is easily plugged which interferes with exposure of the drug to the external fluids.

G. Ranade U. S. Patent No. 4,803,076 (the '076 patent)
K. Cremer U. S. Patent No. 6,264,985 (the '985 patent)

Ranade and Cremer disclose controlled release devices comprising (i) a compressed core which is a truncated cone and (ii) an impermeable wall or coating on the base and side, but not the top, of the truncated cone.

The controlled release device disclosed by Ranade is a truncated cone with top to bottom base diameters of 1:2 to 1:4 and a height to base diameter in the ratio of 1:1 to 1:4, or , in an alternate embodiment the cone my have a convex base to minimize tailing (col. 2, lines 43-45). The core contains the active substance optionally combined with inert ingredients to aid tablet formation (col. 3, lines 9-12). The inert ingredients can be soluble in the fluid medium (i.e., a dissolution device), or they can form an insoluble matrix which retains its shape as the active ingredient dissolves (i.e., a diffusion device) (col. 3, lines 23-27).

The core is coated with a material which is substantially impermeable to the tablet contents and to the GI medium. Ethylene-vinyl acetate copolymers are exemplified (col.6, lines 7-9 and Example 1). The patent also discloses novel methods and equipment to manufacture the tablet. The cores are spray coated by conventional means and an apparatus is described to cut or grind the coating from the exposed surface (col. 6, lines 12-40).

Two earlier, but related patents, which are less similar to the present invention, are D. Brooke U. S. Patent No. 3,851,648 and 3,924,622. H. R. Jacobs, U. S. Patent No. 3,113,076, also represent an earlier prototype which attempts to exploit similar principles.

Present Invention	U. S. Patent No. 4,803,076 U. S. Patent No. 6,264,985
The compositions in claims 1, 22 and 37 have a coating comprised of an insoluble polymer and soluble pore forming materials which dissolve after the core is depleted producing a permeable porous coating that can disintegrate..	Core covered by impermeable coat. No additional excipients are described.
The dimensions in geometries described in FIG. 1a-1f are constant throughout release period and therefore the exposed surface area and the release rate are constant in a dissolution device.	The dimensions of the exposed surface increase, and therefore the surface area exposed to the fluid medium, increases during the drug deliver process. This geometry will not provide zero-order release in a dissolution device.
FIG. 4 provides a geometry which decreases surface area and the release rate over the delivery period in a dissolution device.	Neither the '076 nor the '985 patent provide a means for decreasing the surface area over the delivery period.
FIG 5 provides a non-conical core wherein the surface area increases during the delivery period.	Both the '076 and the '985 are substantially conical cores.

An additional feature of the present invention is a novel coating which surrounds the core during the drug delivery period but disintegrates after the drug is depleted from the core. Coatings containing insoluble polymers and water soluble pore fromng elements were objects of a second separate search. The class/subclasses searched include 424/468, 472, 473, 474, 475, 482, 479, 480 and 481.

Many sustained-release compositions employ impermeable or semi-permeable coatings containing pore-forming substances. Numerous insoluble polymers and pore-forming substances have been described and various coating processes and protocols have been used. Despite extensive efforts, coatings with pore forming particles have not solved the problem of reliable efficient sustained release and there is a continuing need to find coatings with superior properties which are efficient and economical to produce and which impart desirable properties on the sustained release devices.

The documents considered most relevant are compared to the present invention; however, the properties of the coatings, the physical and chemical characteristics of the coating and the processes to apply the coatings in the present invention differ from those found in the prior art. The prior art teachings apply the coating by conventional spray-coating techniques with coating materials containing suspensions or solutions of pore forming substances. Upon drying these form films with pore-forming substances that dissolve or leach out of the coating to form pores or channels for fluids to flow into the device and solutions containing the active ingredient to pass out of the device. Pores in impermeable coatings function as entry and exit passages. Pores in semi-permeable coatings are exit channels for fluids entering through the semi-permeable membrane

The present invention utilizes compression coating to produce a coating which disintegrates after pore-forming materials leach or dissolve out of the coating. In this technique the preformed core is covered with a mixture of the solid coating and solid pore forming compound which are then compressed around the core. The materials are not dissolved in solvents or coated by traditional techniques. This produces superior mechanical bonding and the coatings are not susceptible to stretching which can result in separation from the core. Some cores in the present invention also are scored to secure the coating to the core. The prior art references completely coat the device whereas in the present invention exposed faces are left uncoated. The pore-forming substances are selected to slowly dissolve and form pores after the active ingredient has been delivered. The pores in the present device are not related to drug delivery. Their function is to impart fragility to the membrane after the delivery period and allow it to disintegrate prior to evacuation from the colon. In the case of dissolution devices in which the core dissolves, passage of the intact coating is undesirable and can be uncomfortable. Diffusion devices include an insoluble matrix which remains after delivery of the active ingredient. The coating adds structural stability during the delivery period, however, the coating disintegrates after the active ingredient is delivered. After the coating disintegrates any remaining insoluble matrix collapses and the device is not voided intact.

The prior art considered most relevant are:

Å. R. Lindahl and S. A. B. Erlandsson U. S. Patent No. 4,558,925 (drawn to compositions), 4,629,619 (drawn to methods of producing the composition) and 4,629,620 (drawn to methods of administering a drug)

A sustained-release coated pharmaceutical tablet comprising a drug-containing tablet and a coating or membrane surrounding the same, wherein the coating is water insoluble and insoluble in gastrointestinal fluids and consists essentially of a terpolymer of polyvinyl chloride, polyvinylacetate and polyvinyl alcohol and a water-soluble pore-creating substance randomly distributed in the terpolymer coating.

The patents disclose a mixture of a specific terpolymer and pore-forming particles (col.2, lines 45-65). The advantage of the terpolymer is its tenacious adherence to the tablet surface (col 8, lines 30-34). The pore-forming compound is soluble in the solvent employed for coating the tablet (col. 3, lines 52-54). The dissolution medium then penetrates the pores into the core of the tablet proper and dissolves the drug contained therein (col 8, lines 53-56). The access of the external fluid medium, and therefore the delivery rate, is a function of the volume of fluid able to penetrate through the pores. The coating is applied as suspension or solution of pore-creating substance and a solvent solution of the terpolymer to form a coating fluid and applying the coating fluid in the from of a solution or suspension to the tablet (claim 1, '619 patent).

R. W. Baker and J. W. Brooke U. S. Patent No. 4,687,660

The disclosed device is an osmotic system and therefore differs fundamentally from the present invention. [T]he osmotic gradient which actively brings water in through the semi-permeable membrane thereby increasing the pressure inside the device, resulted in a saturated solution of the beneficial agent bring pumped out through the micropassageways created by the water dissolving the pore-forming, water-soluble particles embedded in the film coating of the device (col. 2, lines 45-53) The polymer solution and the pore-forming material suspension can be separately but simultaneously applied as by spray coating in a pan coater or fluidized bed (col 2, lines 21-25).

P. S.-L. Wong *et al.* U. S. Patent No. 4,783,337

The invention similarly relates to an osmotic delivery device wherein microporous laminae are used to transport fluids. (col. 11, lines 3-68).

J. Kendrup and P. Fyhr, U. S. Patent Application Publication No. US 2001/0038853 A1

The publication discloses a method for producing a controlled-release pharmaceutical preparation with a particle-containing coating, the coating being derived from an aqueous dispersion of film forming water insoluble polymer and a water-soluble pore-forming agent. The method utilizes spray coating techniques (¶ 0032) of film-forming polymer (¶ 0023). Dissolution of the particles creates a network of channels or pores of a predetermined size in the polymer coating and the drug is release through these pores or canals (¶ 0012). The porous coating provides good mechanical stability and the polymer film will be left intact after release of the drug (¶ 0012)

Present Invention	Prior Art
Pores form to allow disintegration of the impermeable coating and spent core of diffusion devices.	Pores formed to provide channels for fluids to flow into and solutions of the active ingredient to flow out of the core.
Applied by compression coating of solid coating and pore-forming particle which does not necessarily form a film.	Typically prepared by spray coating techniques using a solution or suspension of pore-formimg particles and inert coating material. Forms a film.
Pore-forming coating does not cover exposed surface	Entire core typically covered with pore forming coating.
Non-film-forming coatings are not subject to stretching.	Films with plasticizer are prone to stretching
Compressed core can be scored to help anchor the coating.	No scoring of the coated object is described.

Respectfully submitted,
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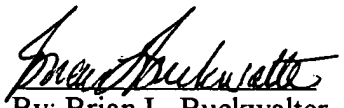

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